REMARKS

Claims 1, 3 – 5 and 7 – 13, as amended, and new claims 14 – 20 are pending in the application. Claims 2 and 6 are canceled without prejudice. The amendments to claim 1 were made to exclude the metabolites of ospemifene and more distinctly define the active compound of the claims. New claims 14 – 20 find support throughout the specification, for example at paragraphs [0021] – [0023]. Therefore, no new matter is added.

Reconsideration and re-examination of this application in view of the following remarks is hereby respectfully requested. Applicant wishes to thank the Examiner for reconsideration and withdrawal of the rejection of claims 1 and 3 – 5 under 35 U.S.C. 102(b) for allegedly being anticipated by Antilla, Head and Neck Cancer (1997) as evidenced by Kangas (1990).

Applicant requests reconsideration and withdrawal of the pending rejections in light of the amendments to the claims and reasons set forth below.

I. REJECTION UNDER 35 U.S.C. §103(a)

Claims 1-5 and 7-13 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Anttila in view of U.S. Pat. No. 6,984,665 ("Blom"). This rejection is respectfully traversed.

First, applicants point out that Blom has an issue date of **January 10, 2006**. Since the instant claims all trace their priority to a date no later than **February 13, 2004** (the filing date of the instant application), Blom is not prior art under either 35 U.S.C. §102(a) or 35 U.S.C. §102(b). Blom is apparent prior art under 35 U.S.C. 102(e). However, since the assignee listed in Blom is Hormos Medical, the same assignee in the instant case, Blom cannot be used for obviousness purposes against the present invention. See 35 U.S.C. §103(c). Because the rejection relies upon a reference that is not prior art, it is deficient and should be withdrawn.

Second, assuming that an equivalent reference is substituted for Blom, such a reference in combination with Antilla would not render obvious the claimed invention. The claimed invention as amended is directed to a method for enhancing the bioavailability of

orally administered ospemifene or a pharmaceutically acceptable salt thereof (hereinafter "ospemifene" unless otherwise noted). The method comprises administering ospemifene orally to an individual in connection with the intake of a foodstuff having nutritional value and causing secretion of bile acids, being taken shortly before, during or shortly after administering the compound to enhance bioavailability of the compound. Dependent claims further specify preferred dosage ranges, preferred isomers of ospemifene, and preferred therapeutic uses of ospemifene The present application discloses that the effect of food intake on ospemifene absorption is 2-3 fold higher than in the fasted state (page 4, lines 4-5). The effect of food also increases the bioavailability of ospemifene in the fed state as compared to the fasted state. (see e.g., Figures 1 and 2).

Antilla teaches that food does not appear to have an effect on the bioavailability of toremifene citrate teaching that the drug "can be taken equally well in fasted conditions or with meals." Blom teaches that ospemifene can be used to treat skin atrophy and epithelial or muscosal atrophy in women. Blom is silent regarding the effect of food on the bioavailability of ospemifene. Therefore, there is nothing in Antilla or Blom, either alone or in combination that teaches or suggests a method for enhancing the bioavailability of orally administered ospemifene.

A finding of obviousness requires that the prior art both suggest the invention and provide one of ordinary skill with a reasonable expectation of success. *In re O'Farrell* 853 F.2d 894, 903, 7 USPQ2d 1673 (Fed. Cir. 1988). Secondary considerations such as unexpected results must be considered if present. *Stratoflex, Inc. v. Aeroquip Corp.,* 713 F.2d 1530, 1538-39, 218 USPQ 871, 879 (Fed. Cir. 1983); *In re Merck & Co., Inc.,* 800 F.2d 1091, 1096, 231 USPQ 375, 378 (Fed. Cir. 1986). The USPTO must consider rebuttal evidence of teaching away. *See In re Sullivan*, 84 USPQ2d 1034, 1038 (Fed. Cir. 2007) (The Federal Circuit remanded an appeal back to the BPAI for failure to consider rebuttal evidence put forth by the Applicant during prosecution).

The Examiner concedes that Antilla does not administer the same drug (i.e. Antilla administers toremifene citrate, not ospemifene). However, the Examiner argues that it is known from Kangas (1990) that toremifene metabolizes into many different active compounds, including ospemifene. The Examiner argues that "[a]dministration of a drug that metabolizes to the active form in vivo is the same as administering the metabolite (i.e.

TORE VI), see Kangas, page 9, Fig. 1) and as claimed." The Examiner acknowledges that the effect of food intake on ospemifene absorption is 2 – 3 fold higher than the fasted state. However, the Examiner deems the results unpersuasive because claim 1 "merely recites inherent properties of the compound" because the administration is allowed to occur "shortly before (i.e., in a fasting mode) or "during or after administering the compound" rather than restricted to a fed state administration.

In reply, applicant disagrees with the Examiner's general point that administering a parent drug that metabolizes to the active form in vivo is the same as administering the active form directly. The statement ignores the specific pharmacokinetic and metabolic differences among drugs in general. With regard to ospemifene, applicant points out that ospemfiene is a minor metabolite of toremifene which does not contribute to the effect of toremifene and its main metabolite desmethyltoremifene as breast cancer treatment compounds. Ospemifene in therapeutic doses demonstrates a therapeutic profile to treat vaginal atrophy, an estrogen agonizing effect, which is an opposite effect versus that of toremifene antagonizing the estrogen effect. Although ospemifene and toremifene are structural relatives, their pharmacokinetics are significantly different: when toremifene has elimination half-life of one week, ospemifene is metabolized much faster, with elimination half-life of one day. The metabolites of ospemifene, 4-OH and 4'-OH ospemifene, are active compounds contributing to the effect of ospemifene in vaginal atrophy, but those metabolites are not formed from toremifene at all.

In addition to the surprising differences in pharmacological and therapeutic effect and metabolism between toremifene and ospemifene, also the absorption shows different characteristics: when food does not have any effect on absorption of toremifene, to applicant's surprise food intake very significantly enhances the absorption of ospemifene, to an extent which has to be considered in the clinical therapy and selecting the effective clinical dose. There is no scientific theory or way to predict such an effect based on the basis of the structures of the compounds. Therefore, administering a parent compound is not the same as administering the metabolite, particularly in the case of toremifene and ospemifene.

Applicant also respectfully disagrees that the claims as amended read on administering ospemifene to a patient in a fasted state. Applicant's studies with

different food compositions (high fat food improving more than low fat food) and the extensive clinical efficacy studies, where applicant has given flexibility in taking an ospemifene tablet within a more broad window around breakfast and measuring enhanced steady-state plasma levels, demonstrate to that biliary secretion is the putative mechanism of the enhanced absorption. The biliary secretion is induced by food fairly quickly after ingestion and the bile-rich environment is maintained in the upper gastrointestinal tract for at least a few hours to digest the food. On the other hand scientific practice is expecting at least an 8 to 12 hour period after food ingestion to reflect the fasting condition. It can be safely expected that at two hours after food ingestion there is still a bile-rich digestive environment in the gastrointestinal tract to enhance ospemifene absorption.

Applicant also points out that ospemifene can be administered shortly before consumption of food which causes biliary secretion and still benefit from enhanced absorption. The reason is that ospemifene shows a relatively slow absorption, the maximum absorbed concentration seen at about two hours, demonstrating that if the food ingestion follows within one hour after ospemifene tablet administration, the absorption enhancement can be safely expected. Therefore, contrary to the Examiner's characterization that the claims encompass "three variables (i.e. shortly before, during, and after)", the claims in fact encompass one variable – a range of time where there is a bile-rich digestive environment in the gastrointestinal tract to enhance ospemifene absorption.

The Examiner also alleges that applicant's rebuttal somehow "concentrates on the single reference Antilla and fails to state why the combination of Antilla and Blom would not have been obvious." Applicant respectfully disagrees. First, as pointed out above, Blom is not prior art. Second, applicant's argument clearly points out that Blom is completely silent regarding the effect of food on the bioavailability of ospemifene. There is nothing to suggest in Blom that administering ospemifene in connection with the intake of a foodstuff having nutritional value and causing secretion of bile acids, being taken shortly before, during or after administering the compound would enhance the oral bioavailability of ospemifene. Therefore one of ordinary skill in the art would have no

reasonable expectation of success that combining Blom with Antilla will achieve the claimed invention.

In light of the amendments and arguments above, applicant respectfully requests reconsideration and withdrawal of the obviousness rejection.

II. FIRST REJECTION FOR OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 1 and 8 – 9 remain rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-12 of U.S. Patent Application No. 11/201,098 (US 2005/0272825). The Office Action maintains the rejection and reasoning that are of record. The Examiner argues that "whether or not the instant claims are directed to bioavailability there is no distinguishing step that indicates once the drug is administered it would not treat skin atrophy." Applicant respectfully disagrees. As pointed out in a prior office action, the Examiner has already taken the position that "food can be an active agent as it comprises nutrients for the functioning of the body." Office Action dated April 30, 2008, page 6. Applicant points out that one distinguishing step between the claimed invention and the prior art is the administration of ospemifene after prompting a bile-rich environment in the gastrointestinal tract. This is simply not a case of inherency despite the Examiner's arguments.

The Examiner has argued that because the FDA sets forth guidance of the food effect on bioavailability of drugs that this would motivate one to combine the prior art references to achieve the claimed invention. Applicant points out that in order for there to be motivation to combine references in a way to suggest a claimed invention, one of ordinary skill in the art must have a reasonable expectation of success. One of ordinary skill in the art had no expectation that administering ospemifene slightly before, during or after food intake would have such a dramatic positive effect on the oral bioavailability of the drug. Rather, the prior art actually taught away from the invention as we have specifically set forth in prior replies. Further, applicant reminds the Examiner that "[p]atentability shall not be negatived by the manner in which the invention was made." 35 U.S.C. 103(a), last sentence.

Applicant respectfully submits that claims 1 and 8 – 9 should not be rejected for obviousness-type double patenting over the '098 patent application,

in view of the teaching away of Anttila, and the unexpected results in disclosed in the specification. Therefore, Applicant respectfully requests that the obviousness-type double patenting rejection of claims 1 and 8 - 9 over US Application No. 11/201,098 be withdrawn.

III. SECOND REJECTION FOR OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 1 – 9 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,984,665 ("the '665 patent"). The Examiner references the arguments already of record and does not provide any new grounds.

In reply, applicant respectfully submits that claims 1 – 9 should not be rejected for obviousness-type double patenting over the '665 patent. For the reasons set forth above in response to the rejection under 35 U.S.C. § 103(a), applicant similarly maintains that claims 1 – 9 should not be rejected for obviousness-type double patenting, in view of the teaching away of Anttila, and the unexpected results in disclosed in the specification. Therefore, Applicant respectfully requests that the obviousness-type double patenting rejection of claims 1 – 9 over the '665 patent be withdrawn.

In view of the above amendments and remarks, it is submitted that the claims are in condition for immediate allowance. The Examiner is invited to contact the undersigned attorneys for the Applicant via telephone if such communication would expedite this application.

Respectfully submitted,

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